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Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study)

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ABSTRACT

Objective: The phase III IUNO trial assessed the benefit of maintenance erlotinib versus erlotinib at progression in advanced/metastatic non-small-cell lung cancer (NSCLC) that had not progressed following four cycles of platinum-based chemotherapy.
Materials and Methods: Patients had stage IIIB/IV NSCLC, no known epidermal growth factor receptor (*EGFR*)-activating mutation, and objective response or disease stabilization after platinum-based induction chemotherapy. Central *EGFR*-mutation testing was undertaken on tumors from patients with unknown or wild-type *EGFR* status following local testing. Patients were randomized to receive blinded maintenance erlotinib 150 mg/day ('early erlotinib') or placebo. Those who progressed on placebo received open-label erlotinib ('late erlotinib'); patients who progressed on erlotinib received approved second-line chemotherapy or best supportive care. Primary endpoint: overall survival (OS).
Results: 643 patients were randomized to receive maintenance erlotinib ($n = 322$) or placebo ($n = 321$). As of March 23, 2015, 242 (75.2%) OS events had occurred with 'early erlotinib' versus 235 (73.2%) with 'late erlotinib'. Median OS was 9.7 and 9.5 months with 'early erlotinib' and 'late erlotinib', respectively (HR, 1.02, 95% CI: 0.85–1.22; log-rank $p = 0.82$). No progression-free survival, objective response rate, or disease control rate benefit was observed with maintenance erlotinib. 410 patients entered the second-line phase of the study: 160 patients (50%) from the maintenance erlotinib arm and 250 patients (78%) from the maintenance placebo arm. The pattern of adverse events (AEs) was consistent with previous trials; 11 patients who received blinded erlotinib and 3 who received placebo died during the blinded maintenance phase due to nontreatment-related AEs.
Conclusions: OS with maintenance erlotinib was not superior to second-line treatment in patients whose tumor did not harbor an *EGFR*-activating mutation. Safety results were consistent with the established safety profile of erlotinib. Thus, maintenance treatment with erlotinib in patients with advanced/metastatic NSCLC without *EGFR*-activating mutations is considered unfavorable.

1. Introduction

The tyrosine kinase inhibitor, erlotinib, is indicated for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*)-activating mutations, for the treatment of patients with locally advanced or metastatic NSCLC after failure

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of at least one prior chemotherapy regimen, and in the European Union for maintenance therapy in patients with locally advanced or metastatic NSCLC with *EGFR*-activating mutations and stable disease (SD) after first-line chemotherapy. In the USA and other countries, the maintenance indication is being revised following the outcome of the study reported here.

Approval of erlotinib in the maintenance setting for locally advanced or metastatic NSCLC was based on the results of the randomized, multicenter, placebo-controlled phase III SATURN trial, which evaluated the efficacy of erlotinib following four cycles of standard platinum-based first-line chemotherapy in patients who had not experienced disease progression or unacceptable toxicity during chemotherapy [1]. Maintenance therapy with erlotinib was well tolerated and significantly prolonged progression-free survival (PFS) compared with placebo in the SATURN trial (hazard ratio [HR] for PFS 0.71, 95% confidence interval [CI]: 0.62–0.82; log-rank $p < 0.0001$) that was conducted in patients who were not selected based on *EGFR*-mutation status.

Here we report the results of a randomized, double-blind, phase III trial (IUNO) that was conducted as a postapproval commitment study, to prospectively determine the relative survival benefit of 'early' maintenance erlotinib therapy (postchemotherapy, but prior to progression) versus 'late' second-line erlotinib therapy (i.e. postprogression) in patients with advanced or metastatic NSCLC whose tumors did not harbor an *EGFR*-activating mutation (exon 19 deletion or exon 21 L858R mutation) and who had not experienced disease progression during four cycles of platinum-based therapy.

2. Materials and methods

2.1. Study design

IUNO was a randomized, double-blind, multicenter, placebo-controlled phase III trial of maintenance erlotinib versus erlotinib at the time of disease progression in patients with advanced NSCLC whose disease had not progressed following platinum-based chemotherapy (ClinicalTrials.gov: NCT01328951; protocol number BO25460). Patients with known *EGFR*-activating mutations were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent prior to any study-related procedures.

2.2. Treatment and study endpoints

The study consisted of four phases: screening, blinded phase, open-label phase, and survival follow-up (Fig. 1). Patients were screened into a chemotherapy run-in period and were required to complete four cycles of an approved noninvestigational platinum-based doublet chemotherapy without disease progression. Eligible patients then entered the blinded phase in which they were randomized 1:1 to receive maintenance erlotinib 150 mg/day orally ('early erlotinib') or placebo ('late erlotinib') until disease progression, death, or unacceptable toxicity. Patients who progressed on placebo during the blinded phase received erlotinib 150 mg/day orally as an open-label second-line treatment until disease progression, death, or unacceptable toxicity. Patients who progressed on erlotinib during the blinded phase received second-line treatment with an approved therapy (e.g. pemetrexed or docetaxel, but not EGFR-directed therapies) or best supportive care (BSC). All patients who completed the blinded and/or open-label study phases entered the survival follow-up phase, unless they withdrew consent for further study participation. Patients who experienced disease progression or unacceptable toxicity during the open-label phase could receive further lines of treatment or BSC. Patients who completed the blinded phase but did not enter the open-label phase could move directly into follow-up and receive BSC (but could still receive further lines of treatment if considered appropriate at any time).

Randomization was stratified according to: histology (squamous vs. nonsquamous); stage (IIIB vs. IV); response to initial chemotherapy (complete response [CR]/partial response [PR] vs. SD); inclusion of bevacizumab in the first-line chemotherapy run-in phase (yes vs. no); smoking status (current vs. former vs. never); and geographical region.

The primary objective of the study was to compare overall survival (OS) with maintenance erlotinib versus second-line erlotinib. Secondary objectives of the study were: to compare PFS, objective response rate (ORR), and disease control rate (DCR) between the study arms (erlotinib vs. placebo) during the blinded maintenance phase; and to evaluate the safety and tolerability profile of erlotinib in this patient population.

2.3. Patients

Males or females aged ≥18 years with advanced/recurrent (stage IIIB) or metastatic (stage IV) NSCLC who had completed four cycles of platinum-based chemotherapy without progression of disease (end of last chemotherapy cycle ≤28 days prior to randomization) were eligible. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

Patients with known *EGFR*-activating mutations (exon 19 deletion and exon 21 L858R mutations) determined by local testing were excluded from the study. Patients with unknown *EGFR*-mutation status or wild-type status determined by local testing were screened and their tumor was tested in a central laboratory (by cobas® EGFR test) to determine their *EGFR*-mutation status or confirm it as wild-type if locally assessed. Patients whose tumors did not harbor an *EGFR*-activating mutation, or those with an indeterminate *EGFR*-mutation status after central testing, were randomized into the blinded phase of the study.

Prior exposure to EGFR inhibitors such as erlotinib, gefitinib, or cetuximab, or prior chemotherapy or systemic antineoplastic therapy for advanced disease before screening was not permitted. Neither was the use of pemetrexed in the maintenance setting (pemetrexed was allowed during the chemotherapy run-in phase). Additional exclusion criteria included: any other malignancies within 5 years, except for curatively resected carcinoma *in situ* of the cervix, basal or squamous cell skin cancer, ductal carcinoma *in situ*, or organ-confined prostate cancer; central nervous system (CNS) metastases or spinal cord compression that had not been definitely treated with surgery and/or radiation, or treated CNS metastases or spinal cord compression without stable disease for ≥2 months; or any unstable systemic disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicated the use of study medication(s) or that might have affected the interpretation of the results or rendered the patient at high risk from treatment complications.

2.4. Statistical considerations

The primary efficacy variable was OS, which was defined as the time from the date of randomization to the date of death, regardless of the cause of death. OS was tested using a two-sided unstratified log-rank test at a 5% significance level. Median survival time was estimated using Kaplan–Meier methodology. Hazard ratios and 95% CIs were estimated by Cox proportional hazard regression. The primary efficacy analysis was planned when 460 events (deaths) had been observed in 610 randomized patients (305 per treatment arm) to ensure 80% power at a two-sided 5% significance level to detect a 30% improvement (HR, 0.77) in OS with maintenance erlotinib

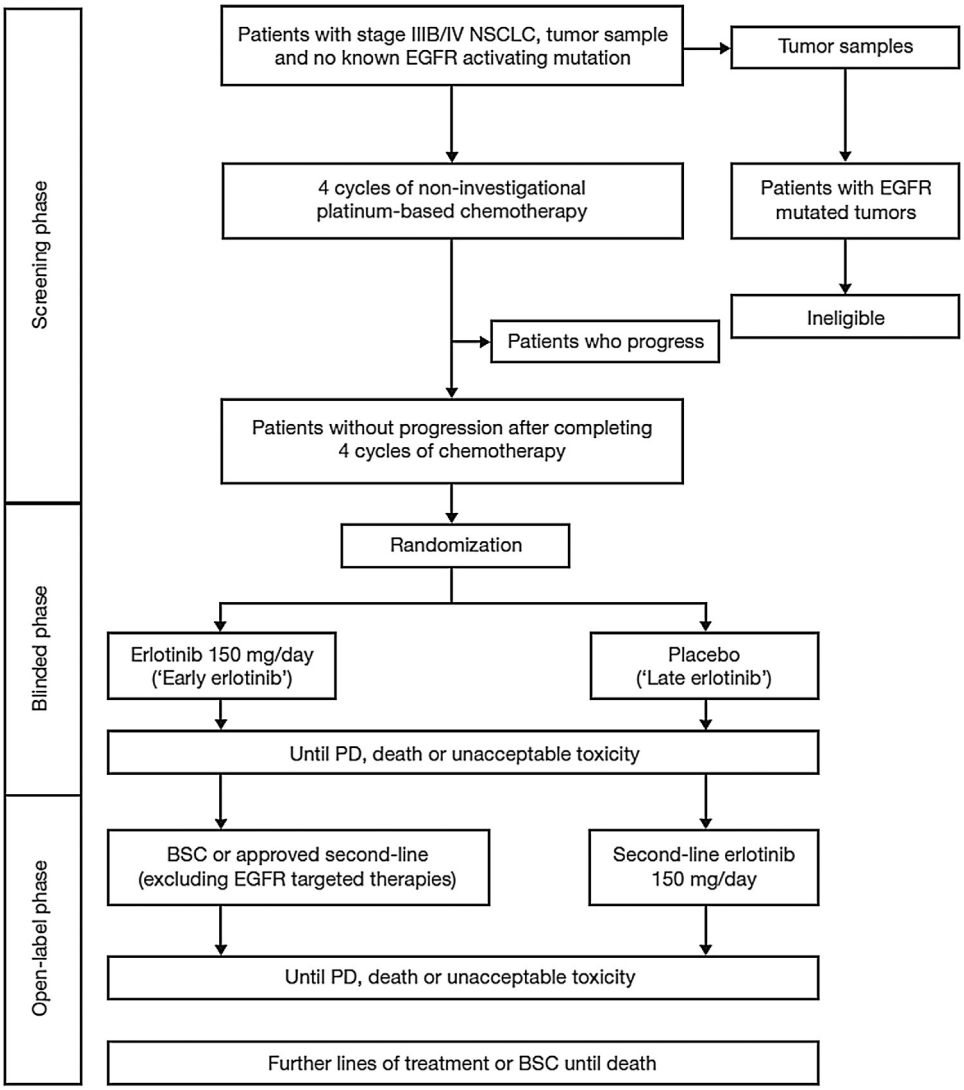

Fig. 1. Study design. BSC = best supportive care, EGFR = epidermal growth factor receptor, NSCLC = non-small-cell lung cancer, PD = progressive disease.

(median OS: 12.5 months) versus second-line erlotinib (median OS: 9.6 months). The cut-off date for the primary analysis was March 23, 2015.

Secondary efficacy variables were PFS, ORR, and DCR in the maintenance setting. Disease progression in the blinded phase was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [2]. Tumor assessments were scheduled at baseline (within a maximum of 2 weeks before starting erlotinib/placebo), Week 6, Week 12, Week 18, and then every 12 weeks until disease progression. Duration of PFS was assessed during the blinded phase of the study, and was defined as the time from randomization to disease progression or death, whichever occurred first.

Subgroup analyses compared OS and PFS in patient groups defined by stratification factors, baseline demographics, and disease characteristics. Forest plots were used to display the HR, 95% CI, and median OS and PFS for each subgroup.

Safety was evaluated by recording and grading adverse events (AEs) in the blinded study phase according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Only serious AEs were collected in the open-label phase of the study and were evaluated separately. Incidences of interstitial lung disease (ILD), an AE of special interest with erlotinib, were also monitored.

All randomized patients were included in the intent-to-treat (ITT) population to assess efficacy endpoints, and all patients who received at least one dose of study treatment were included in the safety analysis population.

3. Results

3.1. Patients

Between September 6, 2011 and June 10, 2014, 1629 patients were screened, of which 643 were randomized to receive maintenance erlotinib ($n = 322$) or placebo ($n = 321$) in the blinded phase of the study (ITT population; Fig. 2). The most frequent reasons for screening failure were: not completing four cycles of platinum-based chemotherapy without progression of disease (29.7%), death during these four cycles of chemotherapy (12.7%), and identification of patients whose tumors were found to harbor an *EGFR*-activating mutation after local testing at screening, or via central testing after screening and prior to randomization (13.0%). In total, 18 patients (5.6%) in the 'early erlotinib' arm and

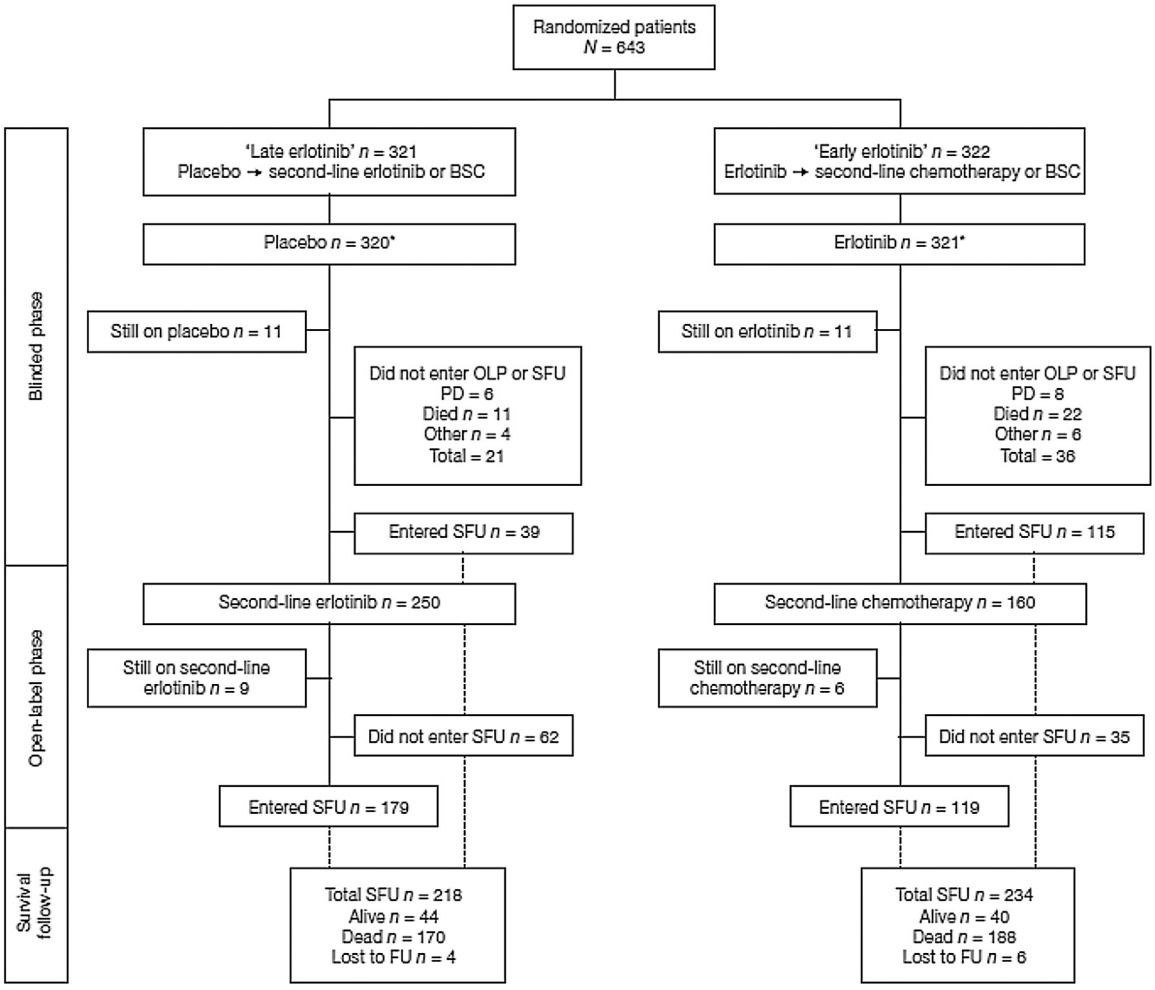

Fig. 2. CONSORT diagram.
*One patient each in the 'early erlotinib' and 'late erlotinib' arms were randomized but did not receive study treatment.
BSC = best supportive care, FU = follow-up, OLP = open-label phase, PD = progressive disease, SFU = survival follow-up.

23 patients (7.2%) in the 'late erlotinib' arm had an indeterminate *EGFR*-mutation status.

Two patients (one in each treatment arm) were excluded from the safety analysis population due to not having received any dose of study treatment. In addition, one patient who was randomized to the placebo arm received erlotinib during the blinded phase and was therefore included in the erlotinib group for safety. The number of patients included in the safety population was 322 and 319 in the maintenance erlotinib and placebo groups, respectively.

Overall, 410 patients entered the open-label second-line phase of the study: 160 patients (50%) from the maintenance erlotinib ('early erlotinib') arm and 250 patients (78%) from the first-line placebo ('late erlotinib') arm (Fig. 2). Two patients who were randomized to the 'late erlotinib' arm received chemotherapy in the open-label phase of the study, even though they received placebo in the blinded phase, and were therefore included in the second-line chemotherapy group for the open-label safety evaluation. The number of patients included in the open-label safety population was 248 and 162 in the second-line erlotinib and chemotherapy groups, respectively.

At data cut-off of March 23, 2015, a total of 84 patients (13%) were alive and in follow-up, and 10 patients (2%) were lost to follow-up (Fig. 2). Overall, 97 patients did not enter the survival follow-up phase. A total of 37 patients were still receiving treatment: 22 in the blinded study phase and 15 in the open-label second-line phase. In the survival follow-up phase, follow-up therapy was received by 85/321 patients (26.5%) in the 'late erlotinib' arm and 84/322 patients (26.1%) in the 'early erlotinib' arm; the most common treatments were taxanes (17.1% vs. 8.7%, respectively), antimetabolites (6.9% vs. 6.5%, respectively), and platinum compounds (5.6% vs. 6.5%, respectively).

Baseline patient and demographic characteristics were balanced between the study arms (Table 1). The median patient age was 61 years (range, 26–86) and most patients had stage IV, nonsquamous disease.

3.2. *Efficacy*

At the data cut-off date of March 23, 2015, 242 OS events (75.2%) had occurred in the 'early erlotinib' arm versus 235 events in the 'late erlotinib' arm (73.2%). Median OS was 9.7 months in patients randomized to 'early erlotinib' and 9.5 months in patients randomized to 'late erlotinib' (HR, 1.02, 95% CI: 0.85–1.22; log-rank $p = 0.82$) (Fig. 3A). The 1-year OS rate was 42% in both treatment arms. Results of subgroup analyses of OS according to stratification factors, demographics, or baseline characteristics, were generally consistent with those in the overall study population (Supplementary Fig. 1). The HR for OS showed a trend in favor of erlotinib maintenance over second-line erlotinib treatment in female patients (HR, 0.78, 95% CI: 0.53–1.13), but no benefit of

Table 1
Patient baseline characteristics.

Characteristic	Placebo (n = 321)	Maintenance erlotinib (n = 322)
Median age, years (range)	61 (30–86)	61 (26–81)
Male/Female, %	76/24	74/26
Stage IIIB/IV, %	22/78	22/78
White/Asian/Other, %	78/21/1	76/22/2
ECOG PS 0/1, %	29/71	28/72
Smoker, %		
Current/Former/Never	57/27/16	58/25/17
Nonsquamous/Squamous, %	64/36	64/36
Response to prior chemotherapy, %		
CR + PR/SD	36/64	36/64
Region, %		
Eastern Europe/South East Asia/Western Europe/Other	55/21/13/11	53/22/14/11

CR = complete response, ECOG PS = Eastern Cooperative Oncology Group performance status, PR = partial response, SD = stable disease.

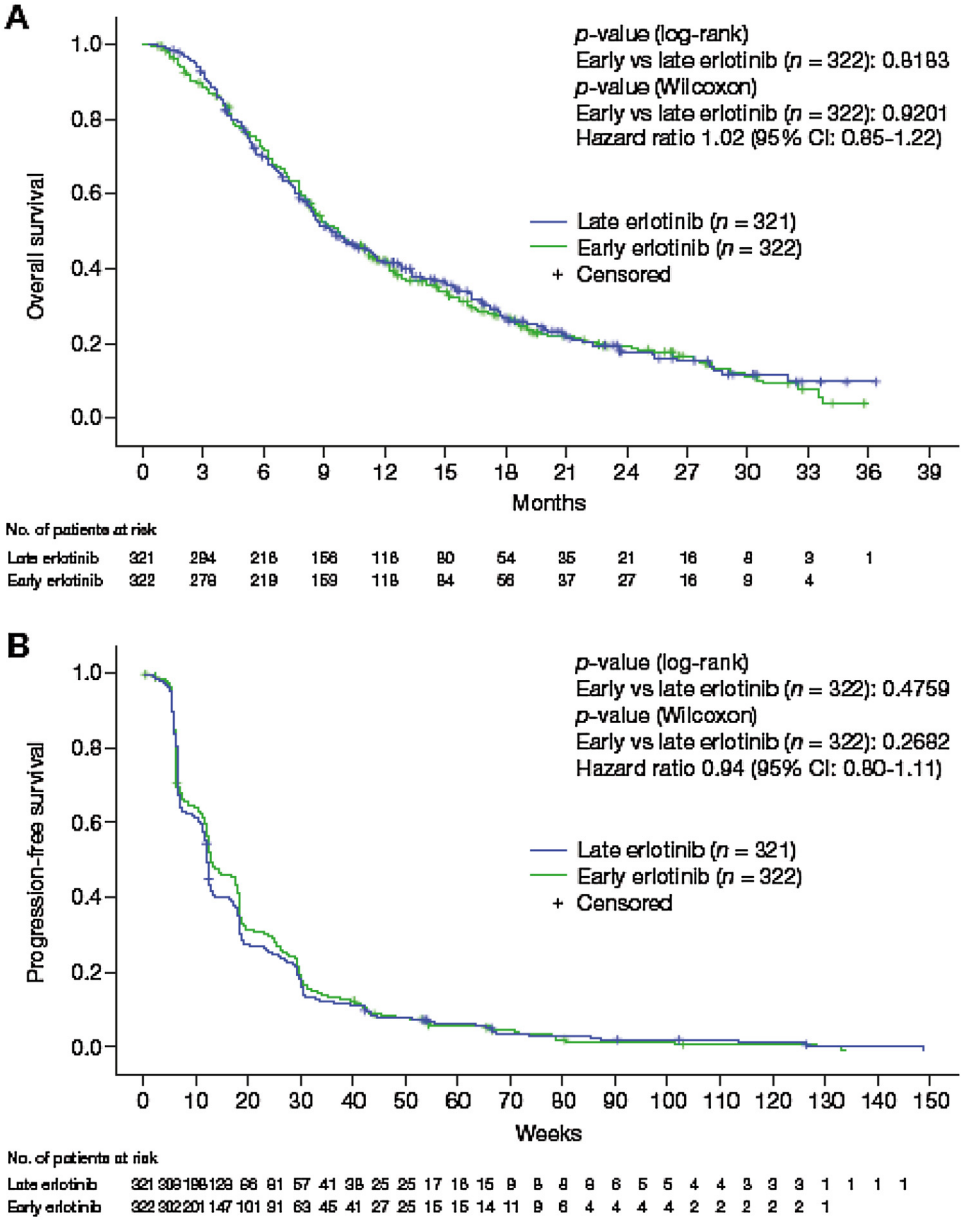

Fig. 3. Kaplan–Meier estimates of (*A*) overall survival and (*B*) progression-free survival during the blinded study phase (ITT population).

Table 2
Secondary efficacy outcomes during the blinded study phase.

Parameter	Placebo (n = 321)		Maintenance erlotinib (n = 322)
ORR			
Responder (CR + PR), n (%) CR PR SD	12 (3.7)2 (0.6)10 (3.1)178 (55.5)		21 (6.5)3 (0.9)18 (5.6)176 (54.7)
Difference in response rate, %		2.78 (−0.78, 6.35)	
P value		0.11	
DCR			
Responder (CR + PR + SD), n (%)	190 (59.2)		197 (61.2)
Difference in response rate		1.99 (−5.74, 9.72)	
P value		0.61	

CR = complete response, DCR = disease control rate, ORR = overall response rate, PR = partial response, SD = stable disease.

maintenance erlotinib was seen in patients with SD (HR, 1.11, 95% CI: 0.88–1.39), although the study was not powered for subgroup analyses.

No meaningful differences were noted in PFS (Fig. 3B), ORR (Table 2), or DCR (Table 2) between the maintenance erlotinib or placebo arms during the blinded phase of the trial. Median PFS was 13.0 weeks with maintenance erlotinib and 12.0 weeks with placebo (HR, 0.94, 95% CI: 0.80–1.11; log-rank $p = 0.48$). The 6-month PFS rate was 24% (95% CI: 19.5–28.9) and 27% (95% CI: 22.2–32.0) in the placebo and erlotinib arms, respectively. Subgroup analyses of PFS were consistent with the results for the overall study population (data not shown).

3.3. Safety

During the blinded phase of the trial, 255 erlotinib-treated patients (79.2%) and 181 placebo-treated patients (56.7%) experienced at least one AE (Table 3). Most AEs were mild or moderate in intensity. Rash (39.4%) and diarrhea (24.2%) were the most frequently reported events with erlotinib. Serious AEs were reported in 36 patients (11.2%) and 27 patients (8.5%) receiving erlotinib and placebo, respectively. Serious AEs resulting in death during the blinded phase occurred in 11 patients (3.4%) in the erlotinib group (three events of pulmonary embolism, two of pneumonia, and one event each of cardiopulmonary failure, cardiorespiratory arrest, cerebrovascular accident, metabolic acidosis, hemoptysis, and aspiration pneumonia) and three patients (0.9%) in the placebo group (lobar pneumonia, hydrocephalus, and respiratory arrest). None of these events was considered causally related to blinded study drug. There were three occurrences of ILD or ILD-like events in two (0.6%) erlotinib-treated patients; although one of these patients had preexisting ILD at baseline.

During the open-label study phase, 23 patients (9.3%) receiving erlotinib and eight patients (4.9%) receiving chemotherapy experienced a serious AE (Table 3). Related serious AEs were reported in 11 patients (4.4%) and two patients (1.2%) receiving erlotinib and chemotherapy, respectively. Serious AEs resulting in death occurred in seven patients (2.8%) in the erlotinib group (pneumonia, aspirational pneumonia, hemoptysis, cardiac failure, jaundice, dyspnea, and unknown cause) and one patient (0.6%) in the chemotherapy group (nosocomial pneumonia). There were no reported cases of ILD in the open-label study phase.

4. Discussion

The aim of the IUNO trial was to determine the relative survival benefit of 'early' maintenance erlotinib treatment versus 'late' second-line erlotinib treatment in patients with advanced or metastatic NSCLC with no known *EGFR*-activating mutations. No OS benefit was observed for maintenance erlotinib versus second-line erlotinib treatment in patients with advanced NSCLC without *EGFR*-activating mutations. Subgroup analyses of OS based on stratification factors, demographics, or baseline characteristics were consistent with the results for the overall population. In female patients, the HR for OS showed a trend in favor of erlotinib maintenance treatment over second-line erlotinib, but no benefit was seen in patients with SD at baseline. This latter result is in contrast to findings of the SATURN study [1], but in-line with data from the randomized phase III IFCT-GFPC 0502 trial of gemcitabine or erlotinib maintenance therapy versus observation in patients with advanced NSCLC, which also included a predefined second-line therapy in the control arm [3].

The discrepancy between the IUNO and SATURN study results with respect to OS improvement may partly be explained by the difference in the proportion of patients receiving second-line erlotinib between the two trials; IUNO included second-line treatment with erlotinib for 78% of patients on the first-line placebo arm, while in SATURN only 21% of patients on the placebo arm received erlotinib as second-line treatment [1]. Furthermore, it is conceivable that the lower sensitivity of the *EGFR* test used in SATURN (Sanger sequencing) may have played a role, together with the fact that *EGFR* mutation status was indeterminate in 4% and 5% of patients on the erlotinib and placebo arms, respectively, and was missing in 12% of patients in each treatment arm [1]. The proportion of patients with indeterminate *EGFR* mutation status after central testing in IUNO was low and comparable in both treatment arms (5.6% in the 'early erlotinib' arm and 7.2% in the 'late erlotinib' arm).

PFS assessed during the blinded maintenance phase was not superior in the erlotinib arm compared with the placebo arm. Similarly, no ORR or DCR benefit was observed in the blinded phase of the trial comparing erlotinib with placebo. Although the open-label phase of the study was controlled for treatment allocation, there was an imbalance in the proportion of patients who received second-line chemotherapy following erlotinib maintenance (50%) compared with those who received second-line erlotinib following placebo maintenance (78%). While the proportion of patients receiving second-line chemotherapy is lower than expected, these figures are comparable with other studies in this setting [1,4]. However, the reasons for not receiving second-line treatment were not prospectively collected and may have been influenced by the fact that chemotherapy was administered in accordance with local practice and reimbursement, while erlotinib was supplied by the Sponsor.

The PFS results in the maintenance phase of this study contrast with the *EGFR* wild-type subgroup findings from the SATURN study, which demonstrated a survival improvement with maintenance erlotinib versus placebo in patients with wild-type *EGFR* status [1,5]. In SATURN, the PFS analysis showed a HR of 0.78 (median 8.9 vs. 12.0 weeks; 95% CI: 0.63–0.96; $p = 0.02$) for the erlotinib group relative to the placebo group, while the secondary endpoint of OS showed a HR of 0.77 (median 10.2 months vs. 11.3 months, 95% CI: 0.61–0.97; $p = 0.02$) [1,5]. A PFS benefit was also reported with maintenance erlotinib in the IFCT-GFPC 0502 trial, with a HR of 0.69 for the erlotinib group versus the observation group (median 2.9 vs.

Table 3
Safety summary during the blinded and open-label study phases.

Blinded phase *n*, (%)	Placebo (*n* = 319)	Maintenance erlotinib (*n* = 322)
Patients with at least one AE	181 (56.7)	255 (79.2)
Total number of AEs	604	962
Patients with at least one:		
AE with fatal outcome	3 (0.9)	11 (3.4)
Serious AE	27 (8.5)	36 (11.2)
Related AE	47 (14.7)	204 (63.4)
Related serious AE	2 (0.6)	6 (1.9)
Grade 3–5 AE	49 (15.4)	77 (23.9)
AE leading to withdrawal from treatment	3 (0.9)	10 (3.1)
AE leading to dose modification/interruption	12 (3.8)	45 (14.0)
AE of special interest (ILD)	0	2 (0.6)
Open-label phase *n*, (%)	Second-line chemotherapy (*n* = 162)	Second-line erlotinib (*n* = 248)
Patients with at least one serious AE	8 (4.9)	23 (9.3)
Total number of serious AEs	12	31
Patients with at least one:		
Serious AE with fatal outcome	1 (0.6)	7 (2.8)
Related serious AE	2 (1.2)	11 (4.4)
Serious AE leading to withdrawal from treatment	1 (0.6)	2 (0.8)
Serious AE leading to dose modification/interruption	3 (1.9)	8 (3.2)

AE = adverse event, ILD = interstitial lung disease.

1.9 months, 95% CI: 0.54–0.88; $p = 0.03$), however, the study was not exclusively conducted in patients with *EGFR* wild-type tumors and included a small number of patients with *EGFR* mutations [3]. The reasons for the lack of PFS benefit with maintenance erlotinib versus placebo in the IUNO study are unclear, but this study demonstrated that there is no discernible maintenance treatment effect in patients with *EGFR* wild-type tumors for inhibition of EGFR by erlotinib when patients have a response or disease control after administration of first-line chemotherapy.

Extrapolation of the blinded phase maintenance results from the IUNO study to treatment in other settings cannot be made. It is important to note that the impact of treatment for patients who have not progressed following chemotherapy (maintenance) may differ from the impact of treatment for patients whose disease is actively progressing (second-line). In addition, although there was an active control in the second-line open-label phase of the IUNO study, no conclusions can be drawn as the study was not designed to comparatively evaluate erlotinib versus chemotherapy in the second-line setting, there was a noticeable imbalance in treatment received, and there was no randomization. The pivotal BR.21 study in patients with stage IIIB/IV NSCLC supports the efficacy and clinical benefit of erlotinib over placebo in the second-line setting, irrespective of *EGFR*-mutation status [6].

Erlotinib was generally well tolerated in the current trial and no new safety signals were identified. Safety results in erlotinib-treated patients were consistent with the safety profile established in previous clinical trials [7,8] and similar to those obtained in the SATURN study [1]. Eleven patients who received 'early erlotinib' during the blinded phase died during the maintenance phase due to an AE compared with three patients who received placebo. None of these events were considered causally related to blinded study drug, but instead were considered related to NSCLC or concurrent conditions. Additionally, most patients had multiple risk factors including relevant comorbidities, smoking, and/or were taking concomitant medications, which may have contributed to the events observed.

In summary, based on the lack of benefit observed in this trial, the use of maintenance treatment with erlotinib in patients with advanced or metastatic NSCLC without *EGFR*-activating mutations is no longer considered to be favorable. The benefit of first-line treatment with erlotinib in patients with advanced NSCLC whose tumors harbor *EGFR*-activating mutations is well established. An improvement in PFS was observed also in the maintenance setting with erlotinib versus placebo in the SATURN study overall and in the *EGFR* mutation-positive subgroup [1]. In light of the results of the IUNO study, the maintenance indication is being revised, and maintenance therapy with erlotinib should only be considered for patients with locally advanced or metastatic NSCLC with *EGFR*-activating mutations.

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Conflicts of interest

Drs. Cicènas, Petrov, and Hotko have no conflicts of interest to disclose; Dr. Geater reports research grants from AstraZeneca, Boehringer Ingelheim, Eisai, Novartis, Roche, and Teva Pharmaceuticals, and honoraria from AstraZeneca, Boehringer Ingelheim, and Roche; Dr. Hooper is an employee of, and owns stock in, Roche Products Ltd.; Dr. Xia is an employee of Roche Product Development; Dr. Mudie is an employee of, and owns stock in, F. Hoffmann-La Roche, Ltd.; Dr. Wu reports payment for participation in speakers' bureaus for AstraZeneca, Eli Lilly, Roche, and Sanofi.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2016.10.007.

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